REMARKS/ARGUMENTS

Reconsideration of the above-identified application respectfully requested.

Claim Amendments

The inadvertent slash is eliminated in Claim 22. Additionally, the list of cytotoxic agents listed in claim 31 has been added in its entirely to claim 22, as has the nomogram of claim 30. Additional cytotoxic agents actually tested are added to claim 26. The administration of suramin has been made mandatory and radiation has been deleted from claim 22.

No new matter is added and entry of these claim amendments respectfully is requested.

The Claim Rejections

Claims 22, 26-28, and 30, and 32-34 stand rejected under the provisions of 33 U.S.C. § 103(a) as being obvious over Agyin (U.S. Patent No. 6,900,235).

Applicants respectfully traverse the rejection of the claims and grounds therefor.

Argument

Briefly, Agyin discloses benzimidazole compounds, and proposes to use these in the treatment of cancer or viral diseases. Use in combination with cytotoxic agents and/or potentiators also is contemplated.

In view of the above-stated new amendments to the claims, the obviousness rejection based on Agyin may have become moot. We, nevertheless traverse this rejection, as follows.

First, Examiner states (page 4, third ¶): "Agyin et al. disclose benzimidazole compounds for the treatment of cancers (Abstract; col. 2, line 39 to col. 3, line 61). The benzimidazole compounds are inhibitors of microtubules as recited in claim 22 (col. 25, lines 43-67; Table 5). The compounds of the invention are disclosed to be useful in combination therapy, such as by combining the benzimidazole compound with a chemotherapeutic agent and/or "potentiator" (col. 17, lines 1-60; col. 23, lines 29-31). A suitable potentiator is suramin as recited in claim 22 (col. 17, lines 56-57)." Applicants respectfully disagree, because, as explained below, Agyin does not teach a suramin combination, and does not teach suramin as a potentiator. Therefore, Agyin does not teach claim 22.

None of Agyin's compounds have antitumor activity in animals bearing transplanted tumors. Agyin provided limited data to support enablement for the treatment of cancers. Cytotoxicity data was presented for 43 benzimidazole compounds and showed IC_{50} concentrations ranging from <10 nM (3 compounds), to >100 μM (6 compounds) (table 4), but none of the compounds tested showed *in vivo* antitumor effect at the highest dose tested (Table

6). As indicated in column 27, line 21, a treatment that causes an increase in lifespan of less than 25% (T/C<125%) is defined as a no activity treatment. All compounds tested showed no activity, except for compound 3-1, which has a T/C value of 132% in one of the four dose levels tested, *i.e.*, 50 mg/kg i.p. However, the other three dose levels, including a higher dose level of 100 mg/kg,i.p., showed inactive T/C values of 97%, 98%, and 108%. No enablement of combinations of benzimidazole compounds with other compounds, such as chemotherapeutic agents or "potentiators" was provided. It is generally known that drugs, which show activity in cultured tumor cells *in vitro*, frequently do not have antitumor activity in animals or human patients. It also is well known that compounds, which are inactive in animal models, are unlikely to be active in human patients. Furthermore, it is unlikely to receive regulatory approval for testing in humans a drug that is without activity in animal models. Therefore, an artisan will not be motivated to use the compounds of Agyin's invention, either singly or in combination, and Agyin does not teach the use of any form of combination therapy.

Agyin does not teach a suramin combination. Agyin proposes to use the benzimidazoles in combination with any chemotherapy agent (column 12, ll. 51-54: "Chemotherapeutic agents used in combination with a compound of the present invention or salt thereof may be selected from any of these groups but are not limited thereto."), or with chemotherapeutic agents and/or potentiators (column 23, ll. 29-32), listing at least 91 compounds as possible "potentiators" (column 17, ll. 1-64). One of the listed compounds is suramin. The number of possible combinations proposed by Agyin, then, is at least (43 * >100 * >91 =) >391,300, where 43 is the number of presented benzimidazole compounds, >100 is the number of chemotherapeutic agents, and >91 is the number of "potentiators" listed. Agyin does not provide the rationale for choosing one combination over the other 390,000+ combinations. Hence, Agyin's proposal to use benzimidazole combinations is merely an invitation to the artisan to search for a possible effective combination from among more than 390,000 possibilities. Accordingly, an artisan would not know which of the >390,000 combinations to study. Even with the teaching of using carboplatin as the cytotoxic to be combined with any one of the 91 potentiators and any one of the 43 benzimidazole compounds, the number of possible combinations is still >3,913, which is still a daunting number that would require substantial and burdensome experimentation. Furthermore, it is well known in the art that there is only a vanishingly small chance of finding a synergistic drug combination, if the search process is a simple random testing of combinations of agents. Hence, an artisan would not be motivated to randomly test combinations. In short, Agyin's disclosure lacks specific and functional steps to enable an artisan to practice Agyin's invention. In fact, an artisan would be discouraged in using Agyin's teaching, since (a) the

benzimidazole compounds are inactive in animal studies, (b) there is no data on possible synergy of any of the combinations is provided, and (c) no other indicators or rationales suggesting a beneficial effect of a combination with benzimidazole compounds were provided. Finally, since Agyin does not teach any combination, he also does not teach a particular combination containing suramin.

Agyin does not teach using suramin as a potentiator. Agyin does not teach using suramin as a potentiator for at least two reasons. First, Applicants have shown that the potentiator effect of suramin happens only at low concentrations (U.S. Patent no. 6,599,912). Suramin does not have sensitization effect at high dose. This shows that the dose is critical to enablement of using suramin. Because Agyin failed to provide the important enablement of the dose requirement, he does not teach using suramin as a potentiator. Second, Agyin does not teach how to obtain the narrow concentration range of 10 to 50 μM maintained over 48 hours that would offer the sensitization effect. As described in the instant application, development of the nomogram for finding the proper suramin dose required many innovative steps and extensive research including experimentation in human patients. Hence, a person with ordinary skills would not be able to combine suramin with the benzimidazole compounds.

The Examiner states (page 4, third ¶): "With regard to claim 26, Agyin et al. teach that carboplatin is a chemotherapeutic agent that may be combined with the disclosed anti-microtubule compounds (Table 3A) and that the compounds of the invention can be combined with chemotherapeutic agents and/or potentiators to provide combination therapy (col. 23, lines 29-3 1). Accordingly, addition of both suramin and carboplatin to a kit comprising an anti-microtubule compound as disclosed in Agyin et al. would have been obvious to one skilled in the art at the time the invention was made." We respectfully disagree, for the following reasons.

Agyin's benzimidazole compounds are not antimicrotubule compounds. As described in Agyin (column 13 l. 39, bridging to column 14, l. 5), tubulin interactive agents act by binding to specific sites on tubulin, inhibiting the formation of microtubules. Microtubules are critical cell structure units. Therefore, anti-tubulin or anti-microtubule agents kill the cell by inhibiting microtubule formation. However, the benzimidazole compounds described in Agyin are not anti-microtubule compounds, for the following reasons. First, the compounds had little activity against microtubule, showing at most mild (≤50%) microtubule inhibition at 2 μM concentration (table 5). Second, a well known pharmacological principle on drug action mechanisms is the cause-and-effect relationship. In other words, if a drug acts by inhibiting a target X, then the inhibition of X is correlated with the treatment outcome. In the case of an anti-microtubule, its inhibition of microtubule should correlate with its cytotoxicity. But such correlation is not found

for benzimidazole compounds; a comparison of the data in table 4 and 5 shows that, *e.g.*, two of the compounds that had no microtubule inhibition (3-9, 3-10) showed cytotoxicity at IC_{50} values of less than 1 μM, whereas the only compound causing 50% inhibition of tubulin polymerization (2-12) did not exhibit cytotoxicity. The weak microtubule inhibition and the lack of correlation between the microtubule inhibition and cytotoxicity indicate that the benzimidazole compounds are generally not anti-microtubule agents.

Applicants' claim 22, from which claim 26 depends, includes: "a cytotoxic agent being one or more of an anti-microtubule agent ...". However, as shown above, the benzimidazole compounds are not anti-microtubule agents. As further shown above, Agyin did not teach any combinations, including combinations with suramin. Furthermore, as shown below, Agyin did not teach kits containing combinations of agents.

Agyin does not teach using kits containing combinations of agents. The Examiner proposes that Agyin's teaching of possible combinations of chemotherapeutic agents and potentiators with anti-microtubule compounds of the invention would make the kit of claim 26 obvious to one skilled in the art at the time the invention was made. Applicants respectfully disagree with this point of view for several reasons. First, Agyin does not propose kits containing combinations of agents (column 24, ll. 6-22; claim 14). He only proposes kits containing a therapeutically effective amount of a benzimidazole. All other components of the kit are optional, and the list of optional components does not include chemotherapeutic agents or potentiators. Therefore, Agyin does not teach kits containing combinations of agents, and certainly not a kit containing a chemotherapeutic agent, suramin, and the instructions as needed to make suramin effective as sensitizer or potentiator of the action of the chemotherapeutic agent.

Second, claim 26 is merely an example of a possible formulation of claim 22 and is dependent of this claim. Therefore, allowance of claim 22 should automatically lead to allowance of claim 26 and the objection is moot.

Third, the instant disclosure is a nomogram that is required to enable the use of the kit containing suramin, which is used to improve the activity of one or more cytotoxic agents, also contained in the kit. The inventive element of instructions that enable application of medicaments, and that provide a functional relationship between the printed matter (instructions) and the claimed kit, is totally lacking in Agyin. His disclosure pertains to a number of compounds of which the utility has not been clearly proven, in spite of his claims to be effective in the treatment of various diseases. In the remainder of his disclosure, he merely postulates that the utility of his compounds could be increased when used in combination with

other compounds. This speculation appears grounded in the widely accepted rule in treatment development for cancer and viral diseases that the most effective therapies for these diseases frequently are combination therapies. This postulated utility, however, in no way anticipates the utility of the nomogram developed for the use of suramin as a sensitizer in the treatment of patients with cancer, and the utility of kits containing the nomogram, suramin, and the chemotherapeutic. As a result, Agyin does not render the current invention obvious, and we respectfully request that the rejection be withdrawn.

With respect to "print instructions", the Examiner has indicated that the nomogram of claim 30 satisfies this requirement. Accordingly, with the addition of the nomogram to kit claim 22, this ground of rejection is moot.

Conclusion

In view of the claim amendments and remarks submitted herewith, allowance of the claims and passage to issue of this application respectfully is requested. If an allowance of the claims is not forthcoming, please enter this amendment for purposes of appeal.

Respectfully submitted,

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